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# Molecular mechanisms and biomedical applications of glucosamine as a potential multifunctional therapeutic agent

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ABSTRACT

Glucosamine and its acetylated derivative, N-acetyl glucosamine, are naturally occurring amino sugars found in human body. They are important components of glycoproteins, proteoglycans and glycosaminoglycans. Scientific studies have supported that glucosamine has the beneficial pharmacological effects to relieve osteoarthritis symptoms. Glucosamine can also be as a promising candidate for the prevention and/or treatment of some other diseases due to its anti-oxidant and anti-inflammatory activities. Most of its function is exerted by modulation of inflammatory responses especially through Nuclear Factor-κB (NF-κB) that can control inflammatory cytokine production and cell survival. In this review, we present a concise update on additional new therapeutic applications of glucosamine including treatment of cardiovascular disease, neurological deficits, skin disorders, cancer and the molecular mechanistic rationale for these uses. This article will also examine safety profile and adverse effects of glucosamine in human.



**Contents**



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## 1. Introduction

Glucosamine (GlcN), 2-amino-2-deoxy-D-glucose, is an essential amino-monosaccharide component of glycoproteins, proteoglycans and glycosaminoglycans. It is the biochemical precursor of all amino sugars in human body. D-Glucosamine is biosynthesized naturally from fructose 6-phosphate and glutamine by glutamine: fructose-6-phosphate aminotransferaseas the first and rate-limiting step of the hexosamine biosynthesis pathway [1]. It is further acetylated to N-acetyl glucosamine (GlcNAc) by glucosamine N-acetyl transferase which is then used for synthesis of glycosylated proteins and lipids (Fig. 1).

In addition to key biochemical functions of GlcN and its acetylated derivative, N-acetyl-D-glucosamine, they have therapeutic potential and are used to prevent or treat a wide variety of diseases and then they are one of the most popular over-the-counter (OTC) supplements in the world. Therefore, economic and high efficiency processes are developed to produce them in an industrial scale [2].

There are three commonly forms of GlcN supplements in the market: glucosamine hydrochloride, glucosamine sulfate, and N-acetyl glucosamine. These glucosamine compounds are usually prepared from chitin through several methods including chemical and enzymatic chitin hydrolysis, and microbial production [3–5]. It has also recently been possible to produce these amino sugars from microbial fermentation processes by fungi or genetically modified bacteria, specifically *Escherichia coli* [6–12].

Glucosamine is mainly administered orally and rarely intravenously or topically. However, there is little information regarding skin absorption and transdermal delivery of GlcN. It seems that glucosamine is poor candidate for transdermal absorption because of its polarity and aqueous solubility [13]. Hence, various formulations of GlcN have been examined in multiple studies for enhancement of skin permeation of this amino sugar [14,15].

Oral GlcN pharmacokinetics data including absorption, distribution, metabolism and excretion (ADME) indicates it has a low and erratic oral bioavailability which is truly unclear in human [2]. Most of these data have been obtained with glucosamine sulfate and there are few studies have been published on the pharmacokinetics of glucosamine hydrochloride in human subjects [16]. Approximately 90% of each oral conventional dose (1500 mg/day) is rapidly absorbed from the gut in human [17]. However, the orally administered glucosamine offers only 20–26% the plasmatic concentrations achieved with intravenous administration [18] that indicates its significant first-pass metabolism and presystematic loss in gut and liver [17]. After adsorption, highest concentration of glucosamine can usually be detected in the liver, kidneys, and cartilages [19] and it has a similar distribution between plasma and synovial fluid [20]. Glucosamine compounds are metabolized in the gut rather than in the liver [2,21,22]. After ingestion, a rapid increase in the plasma level is observed to reach a maximum level of 30 times higher than the baseline [23,24].

The maximum plasma concentration of glucosamine in human healthy subjects is approximately 0.04 mmol/L which following a conventional dose (1500 mg/day) rising up to 0.06 mmol/L [25]. Glucosamine is taken up by cells by glucose transporter proteins but because of its low affinity for these transporters, it seems that the concentration of GlcN in most cells would be lower than that in plasma. To inhibit arthritis in rat, peak plasma concentration should be approximately 16 mg/L, that it is much greater than Cmax following 1500 mg per a day doses in human [22]. So, GlcN should be taken at daily doses of 1500 mg/day for at least 4–8 weeks (a long-course therapy) [24,26] for revealing its optimal health benefits and potentially biomedical effects.

In recent years many efforts have been made to enhance gut absorption and oral bioavailability of glucosamine. This has led to an ongoing search for developing different formulations of this dietary supplement. For example, in vitro and in vivo studies of Qian et al. in animal models showed that chitosan could significantly enhance the oral absorption and plasma concentration of GlcN without altering its elimination [18]. Kohan et.al also synthesized a peptide prodrug of glucosamine which raises its intestinal absorption in vitro. They utilized Glycine-Valine dipeptide conjugation which enhances permeability of GlcN through the gut peptide transporter 1. This prodrug also showed favorable chemical and physical stability [27].

Elimination half-life of GlcN is estimated 15 h [24,28], where GlcN is excreted in the rat feces, urine, and exhaled as much as 2, 40 and 50%, respectively [29]. It is noteworthy that acetylated derivative shows a slight different pharmacokinetic data from glucosamine e.g. it is more excreted in the urine and no radiolabel GlcNAc could be detected in the feces [30].

Glucosamine compounds have been extensively studied for the treatment of many diseases including temporomandibular joint disorders and rheumatoid arthritis. Recently, many researches introduce the novel biological and pharmacological applications of GlcN compounds such as treating skin disorders, cancer, cardiovascular diseases, bacterial infection and etc. (Fig. 2) which will be discussed in detail in this review. It seems that glucosamine exerts its most of functions through suppression of inflammatory pathways, particularly Nuclear Factor-κB (NF-κB) signaling, and a decline in pro-inflammatory cytokines production and enzymes expression.

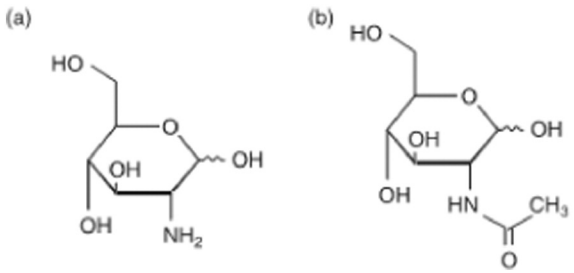


**Fig. 1.** Chemical structure of glucosamine (a) and N-acetyl glucosamine (b).

## 2. Therapeutic applications

### 2.1. Anti-inflammatory and Immunomodulatory effects

There are numerous evidences from in vitro and preclinical studies which indicate the anti-inflammatory and immunosuppressive properties of glucosamine. Osteoarthritis, especially in the knee, is the most common type of arthritis or degenerative joint disease in the elderly [31,32]. This inflammatory disease is accompanied by poor quality of life and economic burden. Therefore, it requires a therapeutic method with minimal side effects, low cost, easy access and benefit in elimination of symptoms. Glucosamine and its derivatives are the most commonly OTC supplements used in treatment of osteoarthritis. The disease-modifying ability of glucosamine in osteoarthritis is mainly attributable to both anti-inflammatory and chondroprotective effects. Several clinical trials and systematic reviews have been conducted on the clinical efficacy of these supplements [33–35]. In brief, these studies